

REMARKS

Claims 1, 4-11, and 13-15 are pending in the instant application. Claims 1, 4-11, and 13-15 stand rejected. Claim 14 stands rejected under 35 U.S.C. §§101 and 112, first paragraph, for depending from a canceled claim. Claims 1, 2, 5-11 and 14 stand rejected under 35 U.S.C. §102(e) as being anticipated by United States Patent Publication No. 2001.0000727 to Driehuys. Claims 3, 4, and 12 stand rejected under 35 U.S.C. §103(a) as being unpatentably over Driehuys and further in view of United States Patent No. 5,245,282 to Mugler. Claim 13 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Driehuys and further in view of WO 99/24080 to Golman et al. The application has been amended. The claims have been amended. Claims 1, 6, 7, 13, and 14 have been amended. Claim 4 has been canceled. New claim 16 has been added. Applicants respectfully submit that none of the amendments constitute new matter in contravention of 35 U.S.C. §132. Reconsideration is respectfully requested.

Applicants respectfully note that the office has rejected claims 2, 3, and 12 even though the Office correctly notes on the Office Action Summary that these claims are no longer pending in the instant application. Applicants will simply deem these rejections as obviated for the purposes of this Response.

Applicant's undersigned counsel also apologizes to the Office for failing to include the claim amendments in the previous Office Action Response to which the Remarks were directed. This oversight is believed to have been the result of a later-discovered word-processing error.

Claim 14 stands rejected under 35 U.S.C. §§101 and 112, first paragraph, for depending from a canceled claim. Applicants respectfully submit that these rejections stand obviated by the amendment to claim 14, making it depend from claim 1. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1 and 5-11 stand rejected under 35 U.S.C. §102(c) as being anticipated by United States Patent No. 6,491,895 to Driehuys et al. This rejection is respectfully traversed.

Claim 1, as amended, recites a method of MR imaging using a hyperpolarized liquid MR imaging agent and wherein spectral-spatial excitation is used in combination with an FISP or PSFI pulse sequence with a flip angle of 45 to 90 degrees.

Driehuys fails to disclose an FISP or PSFI pulse sequence with a flip angle of 45 to 90 degrees which is utilized in the MR imaging in combination with spectral spatial excitation. As even acknowledged by the Examiner on page 5, item 5, none of the mentioned sequences describes a sequence protocol which is identical with a FISP or PSFI pulse. The sequences disclosed by Driehuys are single echo or multi-echo pulse sequences (for instance col. 10, lines 22-24), specifically Echo Planar Imaging (EPI), Rapid Acquisition with Relaxation Enhancement (RARE), Fast Spin Echo (FSE), Gradient Recalled Echoes (GRE) and BEST (col. 14, lines 18-35).

Golman discloses hyperpolarized parahydrogen-labeled agents and their use in MR imaging and is only cited against claim 13.

Mugler is cited for disclosing a FISP or PSIF pulse sequence. The Office, in rejecting previously-pending claim 4 (which is now incorporated into claim 1) under 35 U.S.C. §103(a), states that it is known from Mugler that by using a FISP or PSFI pulse sequence it is possible to compensate for the flow or motion of the blood in the blood vessel.

Applicants respectfully submit, however, that as neither Driehuys, Golman, nor Mugler, either alone or in combination, disclose a hyperpolarized liquid, MR imaging agent wherein spectral-spatial excitation is used in combination with an FISP or PSFI pulse sequence with a flip angle of 45 to 90 degrees.

Moreover, Applicants respectfully submit that there would be no such motivation to apply Mugler in the manner suggested by the Office. Muggler is related to conventional MR imaging agents, i.e. agents which interact with the water-protons naturally found in a patient's body and which affect the relaxation times of those water protons in order to provide contrast in the MR image. Using such conventional MR imaging agents can result in a low signal due to flow or motion of the blood in the blood vessel. Such a low signal due to blood flow, however, is not a problem for hyperpolarized imaging agents. The signal coming directly from the hyperpolarized imaging agent – it can be regarded as a kind of “non-radioactive tracer” - is so much stronger than that from a conventional MR agent due to the fact that little or no background signal interference occurs (due to the very low natural

abundance for nuclei like ^{13}C , ^{15}N or ^{129}Xe). Compensation for flow or motion of blood in the blood vessel is thus of little or no importance. Thus there would have been no motivation to combine Mugler with Driehuys or any hyperpolarized art as suggested by the Office, because hyperpolarized agents do not have the problems of low signal due to motion and blood flow inherent in conventional proton imaging.

Additionally, Applicants respectfully submit that the application of the Mugler pulse sequence is not something that is simply or readily accomplished. A particular problem with hyperpolarized agents is that magnetization of the hyperpolarized nuclei of the agent is destroyed by pulses, meaning that by doing MR imaging one destroys the imaging agent. Importantly, for the signal of the imaging agent, this process is not reversible (i.e., the magnetization of the hyperpolarized agent, once destroyed, cannot be recovered). This is stated in the description of the present application, page 4, 2nd and 3rd paragraph and is also mentioned by Driehuys et al. in col. 4, lines 31-34. Hence pulse sequences have to be carefully chosen when using hyperpolarized MR imaging agents. With conventional agents, such as those used in Mugler, it is not the signal of the agent itself but of its interaction with protons – the proton signals – which are detected. Magnetization of these conventional (Mugler) agents can be recovered by pulses. Thus the application of Mugler's pulse sequences to hyperpolarized agents is not a given because such sequences can destroy the polarization of the hyperpolarized agent.

Yet, even assuming, *arguendo*, that one of ordinary skill in the art would have looked to Mugler, Mugler in fact teaches away from using a 'FISP or PSFI pulse sequence with a

flip angle of 45 to 90 degrees which is utilized in the MR imaging in combination with spectral spatial excitation' as claimed by the present invention. Looking at Example IV, Mugler describes the use of a FISP sequence with a flip angle of 10° (this Example is the only place in Mugler's description where a flip angle for a FISP sequence is stated).

Compare this with Example 3 of the instant application, which compares an image of hyperpolarized ^{13}C using a FISP sequence with a flip angle of 5° with an image using a FISP sequence with a flip angle of 90°, i.e. a sequence according to the claimed invention. As shown in Applicants' Example, with a small flip angle (i.e., in accordance with the teaching of Mugler) contrast was poor. Yet using a larger flip angle (i.e., in accordance with the present invention) obtains a much better contrast. Thus, not only does Mugler not address a concern for hyperpolarized agents, but Mugler's solution teaches away from that provided by the present invention.

Therefore, as none of the cited references, either alone or in combination, would provide a method of MR imaging using a hyperpolarized liquid MR imaging agent wherein spectral-spatial excitation is used in combination with an FISP or PSFI pulse sequence with a flip angle of 45 to 90 degrees, Applicants respectfully submit that the instant invention is patentably distinct thereover. Similarly, as the remainder of the claims are either directly or indirectly dependent on allowable claim 1, Applicants respectfully submit that it is axiomatic that these claims are patentably distinct over the cited art as well. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim 4, stands rejected under 35 U.S.C. §103(a) as being unpatentable over Driehuys as applied to claim 1 and further in view of United States Patent No. 5,245,282 to Mugler, III et al. Applicant respectfully submits that this claim stands obviated by the cancellation of claim 4. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim 13 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Driehuys and further in view of WO 99/24080 to Golman et al. This rejection is respectfully traversed.

Applicants respectfully submit that as claim 13 depends from allowable claim 1, that claim 13 is likewise allowable over the cited art. Reconsideration and withdrawal of the rejection are respectfully requested.

In view of the amendments and remarks hereinabove, Applicant respectfully submits that the present application, including claims 1, 5-11, and 13-16, is in condition for allowance. Favorable action thereon is respectfully requested.

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Any questions with respect to the foregoing may be directed to Applicant's undersigned counsel at the telephone number below.

Respectfully submitted,

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